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COMBINATION OF AN IBAT INHIBITOR AND A METAL SALT FOR THE TREATMENT OF DIARRHOEA

Abstract:

A combination comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, is described. Compositions containing this combination and uses of the combination are also described.

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(54) Title: COMBINATION OF AN IBAT INHIBITOR AND A METAL SALT FOR THE TREATMENT OF DIARRHOEA

(57) Abstract: A combination comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, is described. Compositions containing this combination and uses of the combination are also described.

WO 2004/006899 A1

# COMBINATION OF AN IBAT INHIBITOR AND A METAL SALT FOR THE TREATMENT OF DIARRHOEA

The present invention relates to combination treatments comprising a metal salt and compounds that possess ileal bile acid transport (IBAT) inhibitory activity wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon. These combination treatments are useful in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an effective amount an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm-blooded animal, such as man. The invention also relates to pharmaceutical compositions containing these combinations and to their use in the manufacture of medicaments. These combinations have value in the treatment of disease states associated with hyperlipidaemic conditions.

It is well-known that hyperlipidaemic conditions associated with elevated concentrations of total cholesterol and LDL cholesterol are major risk factors for cardiovascular atherosclerotic disease (Circulation 1999, 100, 1930-1938 and Circulation, 1999, 100, 1134-46). To reduce the risk and the total mortality due to cardiovascular disease, the reduction of plasma lipids, particularly LDL cholesterol, is now recognized as an important therapeutic goal (N Engl J Med. 1995; 332:5, 12-21).

Interfering with the circulation of bile acids within the lumen of the intestinal tracts has also been found to reduce the level of cholesterol. Bile acids are synthesized in the liver from cholesterol and secreted into the bile. They are actively recycled (>95%) from the small intestine back to the liver. Previous established therapies have involved, for example, treatment with bile acid binders, such as resins. Frequently used bile acid binders are for instance cholestyramine and cholestipol.

Another proposed therapy (Current Opinion on Lipidology, 1999, 10, 269-74) involves the treatment with substances with an IBAT inhibitory effect. Theoretically, IBAT inhibitors should have similar therapeutic effect as the resins but they might also be expected to have attractive advantages. First, it should be possible to administer IBAT inhibitors as tablets at the same dose intervals as statins. Second, a direct inhibition of the transport of bile acids across the ileum should be advantageous in situations when IBAT is upregulated. However, available data on the effects of IBAT inhibitors is limited. Several IBAT agents have previously been shown to promote the faecal excretion of bile acids and to reduce plasma cholesterol. The proposed mechanism for the hypolipidaemic action of these

compounds is by an induced number of hepatic LDL receptors due to the increased consumption of hepatic cholesterol caused by a compensatory increased bile acid synthesis (Arterioscler Thromb Vasc Biol. 1998; 18: 1304-11).

However, bile acids that are not recycled in the intestines induce irritation of the intestinal luminal surfaces, at least at higher concentrations. This is seen for example in chronic diarrhoea, and in post infectious diarrhoea with deficient uptake of bile acids, after continuous bile acid secretion following cholecystectomy and after resection of the distal ileum. *In vivo* dosing of IBAT compounds may give rise to these side effects either in certain patients or at high enough doses, i.e. irritation of the intestine would be induced, resulting in diarrhoea. The present invention ameliorates this problem.

Furthermore, if chronic diarrhoea was a side effect, then it is possible that these compounds would not be suitable for administering to patients at all (or at least at high enough doses to give a therapeutic effect), despite their efficacy. The present invention therefore provides the additional advantage that it opens up treatment with an IBAT inhibitor to a particular patient population where it might otherwise have not been possible to use these compounds.

Patients suffering from bile acid induced diarrhoea caused by intestinal bypass for example have previously been treated with large doses (2-4 g) of a calcium salt (Reference: Steinbach et al Eur. J of Gastroenterology & Hepathology 1996, 8:559-562). A 2-4 g dose of a salt is too large for convenient dosing regimen, and patient compliance with this regime would be in doubt. This dose is also too large to make a single tablet made up of the IBAT inhibitor and the salt, which is one aspect of the present invention. A formulation which delivers the metal salt with a targeted release to the terminal ileum, caecum and/or the colon would allow a much lower dose of the salt to be used because there will be no loss of the metal salt due to absorption or binding to other components in the small intestine. Therefore it should be possible to formulate a convenient combination regimen, either a single combination tablet or otherwise.

In the literature IBAT inhibitors are often referred to by different names. It is to be understood that where IBAT inhibitors are referred to herein, this term also encompasses compounds known in the literature as:

i) ileal apical sodium co-dependent bile acid transporter (ASBT) inhibitors;

ii) bile acid transporter (BAT) inhibitors;

iii) ileal sodium/bile acid cotransporter system inhibitors;

iv) apical sodium-bile acid cotransporter inhibitors;

v) ileal sodium-dependent bile acid transport inhibitors;

vi) bile acid reabsorption (BARI's) inhibitors; and

vii) sodium bile acid transporter (SBAT) inhibitors;

where they act by inhibition of IBAT.

Accordingly the present invention provides a combination which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

The present inventors have found that there are at least two mechanisms behind the calcium induced bile acid binding. Firstly, bile acids may adsorb to calcium phosphate particles, and, secondly, unconjugated bile acids may form insoluble calcium salts of bile acids.

Herein, where the term "combination" is used it is to be understood that this refers to simultaneous, separate or sequential administration. In one aspect of the invention "combination" refers to simultaneous administration. In another aspect of the invention "combination" refers to separate administration. In a further aspect of the invention "combination" refers to sequential administration. Where the administration is sequential or separate, the delay in administering the second component should not be such as to lose the benefit of the combination.

The combination of the present invention may either be in the form of a fixed combination with the IBAT inhibitor, in which case both the IBAT inhibitor and the metal salt are formulated to release in the terminal ileum, caecum and/or the colon, or a free combination wherein only the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

In one aspect, the metal salt is formulated to release in the terminal ileum. In a further aspect the metal salt is formulated to release in the caecum. In another aspect of the invention, the metal salt is formulated to release in the colon. In one aspect, the metal salt is formulated to release in the terminal ileum and the caceum. In a further aspect the metal salt is formulated to release in the caecum and the colon. In another aspect of the invention, the metal salt is formulated to release in the terminal ileum and the colon. In another aspect of the invention the metal salt is formulated to release in the terminal ileum, caecum and the colon.

In another aspect where the metal salt is formulated to release in a specified site, i.e. the terminal ileum, caecum and/or the colon, particularly greater than 50% of the metal salt is released here. More particularly this is greater than 70%. More particularly this is greater than 90%. More particularly this is greater than 95%. More particularly this is greater than 99%.

Suitable metals in the metal salt include any pharmaceutically acceptable multivalent metal ion. In one aspect of the invention these metals are calcium, aluminium, iron, copper, zinc, magnesium, manganese or tin salts. In another aspect of the invention these metals are Ca(II), Al(III), Fe(II), Fe(III), Cu(II), Zn(II), Mg(II), Mn(II) or Sn(II) salts. In a further aspect of the invention the metal in the metal salt is calcium. In another aspect the metal in the metal salt is Ca(II). The salt may be any suitable pharmaceutically acceptable salt. In one aspect the salt is acetate, ascorbate, carbonate, chloride, citrate, gluconate, lactate, nitrate, oxalate, phosphate or sulphate. Suitable metal salts include calcium phosphate, calcium lactate, calcium carbonate, calcium gluconate and calcium acetate, particularly calcium phosphate.

It is to be understood that the combination of the present invention includes the situation where there is one metal salt in the combination with the IBAT inhibitor. In addition the combination of the present invention includes the situation where there are one or more metal salts in the combination with the IBAT inhibitor. In this case the salts may be one or more different salts of the same metal, one or more of the same salt of different metals or one or more different salts of different metals.

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/38182, WO 98/40375, WO 99/35135, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 00/47568, WO 00/61568, WO 01/66533, DE 19825804, and EP 864 582 and the contents of these patent applications are incorporated herein by reference. Particularly the named examples of these patent applications are incorporated herein by reference. More particularly claim 1 of these patent application are incorporated herein by reference.

Further suitable compounds possessing IBAT inhibitory activity have been described in WO 94/24087, WO98/07749, WO 98/56757, WO 99/32478, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 00/35889, WO 01/34570, WO01/68096, WO 01/68637, WO 02/08211, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 489 423, EP 549 967, EP 573 848, EP 624 593, EP 624 594, EP 624 595, EP 869 121 and EP 1 070 703.

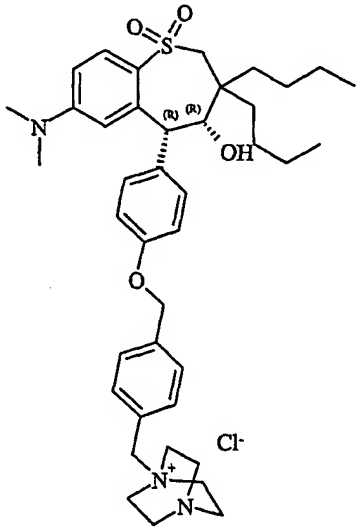
Particularly the named examples of these patent applications are incorporated herein by reference. More particularly claim 1 of these patent application are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582).

A further suitable compound possessing IBAT inhibitory activity is S-8921 (EP 597 107).

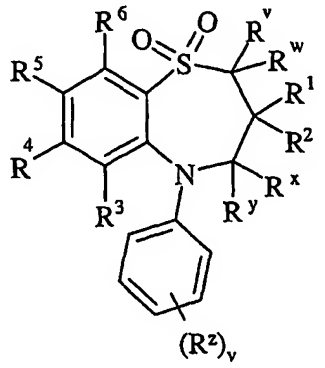
A further suitable IBAT inhibitor is the compound:



WO 99/32478

Other suitable IBAT inhibitors are those described in WO 01/66533. A particular compound of the invention is selected from any one of Example 1-39 of WO 01/66533, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-39 are incorporated herein by reference. Claims 1-6 of WO 01/66533 are also incorporated herein by reference.

Additional suitable IBAT inhibitors are those described in WO 02/50051. Additional suitable compounds possessing IBAT inhibitory activity have the following structure of formula **(AI)**:



**(AI)**

wherein:

$\mathbf{R^v}$ and $\mathbf{R^w}$ are independently selected from hydrogen or $C_{1-6}$alkyl;

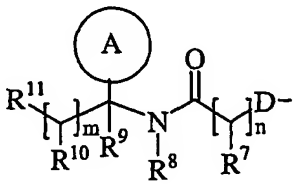
$\mathbf{R^1}$ and $\mathbf{R^2}$ are independently selected from $C_{1-6}$alkyl;

$\mathbf{R^x}$ and $\mathbf{R^y}$ are independently selected from hydrogen or $C_{1-6}$alkyl, or one of $R^x$ and $R^y$ is hydrogen or $C_{1-6}$alkyl and the other is hydroxy or $C_{1-6}$alkoxy;

$\mathbf{R^z}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, $C_{1-6}$alkoxycarbonylamino, ureido, *N'*-($C_{1-6}$alkyl)ureido, *N*-($C_{1-6}$alkyl)ureido, *N',N'*-($C_{1-6}$alkyl)$_2$ureido, *N'*-($C_{1-6}$alkyl)-*N*-($C_{1-6}$alkyl)ureido, *N',N'*-($C_{1-6}$alkyl)$_2$-*N*-($C_{1-6}$alkyl)ureido, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

**v** is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula **(AIA)**:



**(AIA)**

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl,

$C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^3$ and $R^6$ and the other of $R^4$ and $R^5$ may be optionally substituted on carbon by one or more $R^{16}$;

**D** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from $R^{17}$;

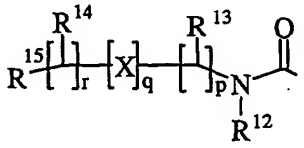
$\mathbf{R^7}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^7$ is optionally substituted by one or more substituents selected from $R^{18}$;

$\mathbf{R^8}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^9}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{10}}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{10}$ is optionally substituted by one or more substituents selected from $R^{19}$;

$\mathbf{R^{11}}$ is carboxy, sulpho, sulphino, phosphono, tetrazolyl, -P(O)(OR$^c$)(OR$^d$), -P(O)(OH)(OR$^c$), -P(O)(OH)(R$^d$) or -P(O)(OR$^c$)(R$^d$) wherein $R^c$ and $R^d$ are independently selected from $C_{1-6}$alkyl; or $R^{11}$ is a group of formula **(AIB)**:



**(AIB)**

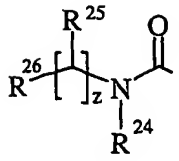
wherein:

**X** is –N($R^q$)-, -N($R^q$)C(O)-, -O-, and -S(O)$_a$-; wherein a is 0-2 and $R^q$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{12}}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are independently selected from hydrogen, $C_{1-4}$alkyl, carbocyclyl, heterocyclyl or $R^{23}$; wherein said $C_{1-4}$alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from $R^{20}$;

$\mathbf{R^{15}}$ is carboxy, sulpho, sulphino, phosphono, tetrazolyl, -P(O)(OR$^e$)(OR$^f$), -P(O)(OH)(OR$^e$), -P(O)(OH)(R$^e$) or -P(O)(OR$^e$)(R$^f$) wherein $R^e$ and $R^f$ are independently selected from $C_{1-6}$alkyl; or $R^{15}$ is a group of formula **(AIC)**:



(AIC)

wherein:

$R^{24}$ is selected from hydrogen or $C_{1-4}$alkyl;

$R^{25}$ is selected from hydrogen, $C_{1-4}$alkyl, carbocyclyl, heterocyclyl or $R^{27}$; wherein said $C_{1-4}$alkyl, carbocyclyl or heterocyclyl may be independently optionally substituted by one or more substituents selected from $R^{28}$;

$R^{26}$ is selected from carboxy, sulpho, sulphino, phosphono, tetrazolyl, -P(O)($OR^g$)($OR^h$), -P(O)(OH)($OR^g$), -P(O)(OH)($R^g$) or -P(O)($OR^g$)($R^h$) wherein $R^g$ and $R^h$ are independently selected from $C_{1-6}$alkyl;

**p** is 1-3; wherein the values of $R^{13}$ may be the same or different;

**q** is 0-1;

**r** is 0-3; wherein the values of $R^{14}$ may be the same or different;

**m** is 0-2; wherein the values of $R^{10}$ may be the same or different;

**n** is 1-3; wherein the values of $R^7$ may be the same or different;

**z** is 0-3; wherein the values of $R^{25}$ may be the same or different;

$R^{16}$, $R^{17}$ and $R^{18}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^{16}$, $R^{17}$ and $R^{18}$ may be independently optionally substituted on carbon by one or more $R^{21}$;

$R^{19}$, $R^{20}$, $R^{23}$, $R^{27}$ and $R^{28}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl, *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)($OR^a$)($OR^b$), -P(O)(OH)($OR^a$), -P(O)(OH)($R^a$) or -P(O)($OR^a$)($R^b$), wherein $R^a$ and $R^b$ are

independently selected from $C_{1-6}$alkyl; wherein $R^{19}$, $R^{20}$, $R^{23}$, $R^{27}$ and $R^{28}$ may be independently optionally substituted on carbon by one or more $R^{22}$;

$R^{21}$ and $R^{22}$ are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additionally suitable IBAT inhibitor are selected from any one of Example 1-120 of WO 02/50051, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-120 are incorporated herein by reference. Claims 1-14 of WO 02/50051 are also incorporated herein by reference. Particular compounds of formula **(AI)** are:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

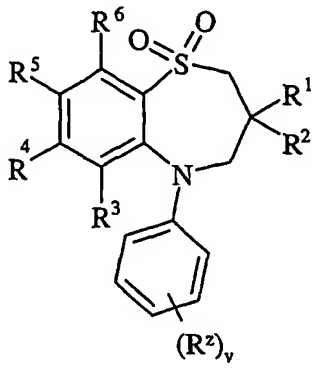
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; and

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additional suitable IBAT inhibitors are those described in WO 03/020710. Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (**BI**):



**(BI)**

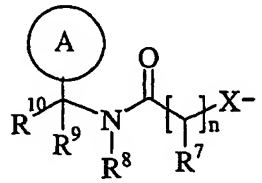
wherein:

One of $\mathbf{R^1}$ and $\mathbf{R^2}$ are selected from hydrogen or $C_{1-6}$alkyl and the other is selected from $C_{1-6}$alkyl;

$\mathbf{R^z}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula (**BIA**):



**(BIA)**

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl; wherein $R^3$ and $R^6$ and the other of $R^4$ and $R^5$ may be optionally substituted on carbon by one or more $R^{17}$;

**X** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

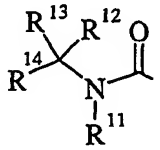
**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from $R^{18}$;

$R^7$ is hydrogen, $C_{1-6}$alkyl, carbocyclyl or heterocyclyl; wherein $R^7$ is optionally substituted on carbon by one or more substituents selected from $R^{19}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{20}$;

$R^8$ is hydrogen or $C_{1-6}$alkyl;

$R^9$ is hydrogen or $C_{1-6}$alkyl;

$R^{10}$ is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclyl, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_p$-$R^{21}$-($C_{1-10}$alkylene)$_q$- or heterocyclyl-($C_{1-10}$alkylene)$_r$-$R^{22}$-($C_{1-10}$alkylene)$_s$-; wherein $R^{10}$ is optionally substituted on carbon by one or more substituents selected from $R^{23}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{24}$; or $R^{10}$ is a group of formula **(BIB)**:



**(BIB)**

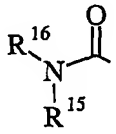
wherein:

$R^{11}$ is hydrogen or $C_{1-6}$alkyl;

$R^{12}$ and $R^{13}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$

wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, carbocyclyl or heterocyclyl; wherein $R^{12}$ and $R^{13}$ may be independently optionally substituted on carbon by one or more substituents selected from $R^{25}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{26}$;

**$R^{14}$** is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclyl, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_p$-$R^{27}$-($C_{1-10}$alkylene)$_q$- or heterocyclyl-($C_{1-10}$alkylene)$_r$-$R^{28}$-($C_{1-10}$alkylene)$_s$-; wherein $R^{14}$ may be optionally substituted on carbon by one or more substituents selected from $R^{29}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{30}$; or $R^{14}$ is a group of formula (**BIC**):



**(BIC)**

**$R^{15}$** is hydrogen or $C_{1-6}$alkyl;

**$R^{16}$** is hydrogen or $C_{1-6}$alkyl; wherein $R^{16}$ may be optionally substituted on carbon by one or more groups selected from $R^{31}$;

**n** is 1-3; wherein the values of $R^7$ may be the same or different;

**$R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ or $R^{31}$** are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl,

carbocyclyl$C_{1-10}$alkyl, heterocyclyl, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_p$-$R^{32}$-($C_{1-10}$alkylene)$_q$- or heterocyclyl-($C_{1-10}$alkylene)$_r$-$R^{33}$-($C_{1-10}$alkylene)$_s$-; wherein $R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ or $R^{31}$ may be independently optionally substituted on carbon by one or more $R^{34}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{35}$;

**$R^{21}$, $R^{22}$, $R^{27}$, $R^{28}$, $R^{32}$ or $R^{33}$** are independently selected from -O-, -$NR^{36}$-, -$S(O)_x$-, -$NR^{36}C(O)NR^{36}$-, -$NR^{36}C(S)NR^{36}$-, -OC(O)N=C-, -$NR^{36}C(O)$- or -$C(O)NR^{36}$-; wherein $R^{36}$ is selected from hydrogen or $C_{1-6}$alkyl, and x is 0-2;

**p**, **q**, **r** and **s** are independently selected from 0-2;

**$R^{34}$** is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-methylsulphamoylamino and *N,N*-dimethylsulphamoylamino;

**$R^{20}$, $R^{24}$, $R^{26}$, $R^{30}$ or $R^{35}$** are independently selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Further suitable IBAT inhibitors are selected from any one of Example 1-44 of WO 03/020710, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-44 are incorporated herein by reference. Claims 1-10 of WO 03/020710 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/020710 is any one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-((S)-1-carbamoyl-2-hydroxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(hydroxycarbamoyl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pyrimidin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(*N'*-pyridin-2-ylureido)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(1-*t*-butoxycarbonylpiperidin-4-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2,3-dihydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N'*-[2-(3,4-dihydroxyphenyl)-2-methoxyethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine

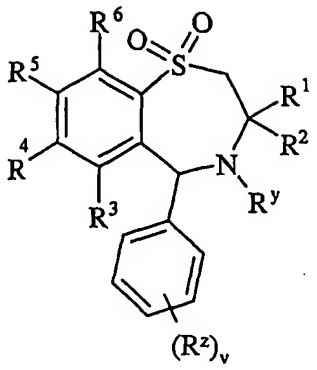
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-aminoethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(piperidin-4-ylmethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-*N*,*N*-dimethylaminosulphamoylethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additional suitable IBAT inhibitors are those described in WO 03/022825. Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (**CI**):



**(CI)**

wherein:

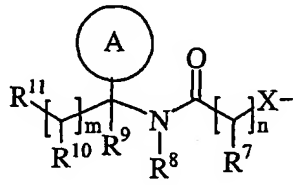
One of $\mathbf{R^1}$ and $\mathbf{R^2}$ are selected from hydrogen or $C_{1-6}$alkyl and the other is selected from $C_{1-6}$alkyl;

$\mathbf{R^y}$ is selected from hydrogen, hydroxy, $C_{1-6}$alkyl, $C_{1-4}$alkoxy and $C_{1-6}$alkanoyloxy;

$\mathbf{R^z}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula **(CIA)**:



**(CIA)**

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^3$ and $R^6$ and the other of $R^4$ and $R^5$ may be optionally substituted on carbon by one or more $R^{16}$;

**X** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from $R^{17}$;

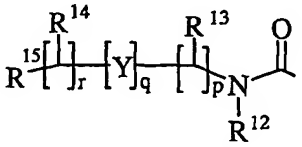
$\mathbf{R^7}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^7$ is optionally substituted by one or more substituents selected from $R^{18}$;

$\mathbf{R^8}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^9}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{10}}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{10}$ is optionally substituted by one or more substituents selected from $R^{19}$;

$\mathbf{R^{11}}$ is carboxy, sulpho, sulphino, phosphono, -P(O)($OR^c$)($OR^d$), -P(O)(OH)($OR^c$), -P(O)(OH)($R^d$) or -P(O)($OR^c$)($R^d$) wherein $R^c$ and $R^d$ are independently selected from $C_{1-6}$alkyl; or $R^{11}$ is a group of formula (**CIB**):



**(CIB)**

wherein:

**Y** is –N($R^x$)-, -N($R^x$)C(O)-, -O-, and -S(O)a-; wherein a is 0-2 and $R^x$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{12}}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are independently selected from hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{13}$ and $R^{14}$ may be independently optionally substituted by one or more substituents selected from $R^{20}$;

$\mathbf{R^{15}}$ is carboxy, sulpho, sulphino, phosphono, -P(O)($OR^e$)($OR^f$), -P(O)(OH)($OR^e$), -P(O)(OH)($R^e$) or -P(O)($OR^e$)($R^f$) wherein $R^e$ and $R^f$ are independently selected from $C_{1-6}$alkyl;

**p** is 1-3; wherein the values of $R^{13}$ may be the same or different;

**q** is 0-1;

**r** is 0-3; wherein the values of $R^{14}$ may be the same or different;

**m** is 0-2; wherein the values of $R^{10}$ may be the same or different;

**n** is 1-3; wherein the values of $R^7$ may be the same or different;

$\mathbf{R^{16}}$, $\mathbf{R^{17}}$ and $\mathbf{R^{18}}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino,

$C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^{16}$, $R^{17}$ and $R^{18}$ may be independently optionally substituted on carbon by one or more $R^{21}$;

**$R^{19}$** and **$R^{20}$** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl, *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR$^a$)(OR$^b$), -P(O)(OH)(OR$^a$), -P(O)(OH)(R$^a$) or -P(O)(OR$^a$)(R$^b$), wherein R$^a$ and R$^b$ are independently selected from $C_{1-6}$alkyl; wherein $R^{19}$ and $R^{20}$ may be independently optionally substituted on carbon by one or more $R^{22}$;

**$R^{21}$** and **$R^{22}$** are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor is one selected from Example 1-7 of WO 03/022825, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-7 are incorporated herein by reference. Claims 1-8 of WO 03/022825 are also incorporated herein by reference. A particular IBAT inhibitor selected from WO 03/022825 is any one of:

1,1-dioxo-3(R)-3-butyl-3-ethyl-5-(R)-5-phenyl-8-[*N*-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3(S)-3-butyl-3-ethyl-5-(S)-5-phenyl-8-[*N*-((R)-α-carboxybenzyl) carbamoylmethoxy]-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3(R)-3-butyl-3-ethyl-5-(R)-5-phenyl-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3(S)-3-butyl-3-ethyl-5-(S)-5-phenyl-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-bromo-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-(S)-3-ethyl-3-butyl-4-hydroxy-5-(S)-5-phenyl-7-bromo-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine

3,5-*trans*-1,1-dioxo-3-(R)-3-ethyl-3-butyl-4-hydroxy-5-(R)-5-phenyl-7-bromo-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

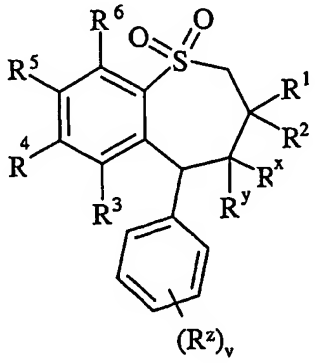
3,5-*trans*-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine ammonia salt;

1,1-dioxo-3-(S)-3-ethyl-3-butyl-5-(S)-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine diethylamine salt; and

1,1-dioxo-3-(R)-3-ethyl-3-butyl-5-(R)-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine diethylamine salt;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additional IBAT inhibitors are those described in WO 03/022830. Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula **(DI)**:




**(DI)**

wherein:

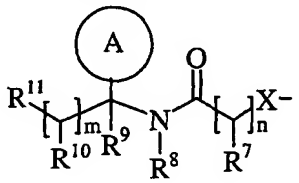
One of $R^1$ and $R^2$ are selected from hydrogen or $C_{1-6}$alkyl and the other is selected from $C_{1-6}$alkyl;

$R^x$ and $R^y$ are independently selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2;

$R^z$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

v is 0-5;

one of $R^4$ and $R^5$ is a group of formula **(DIA)**:




**(DIA)**

$R^3$ and $R^6$ and the other of $R^4$ and $R^5$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^3$ and $R^6$ and the other of $R^4$ and $R^5$ may be optionally substituted on carbon by one or more $R^{16}$;

**X** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from $R^{17}$;

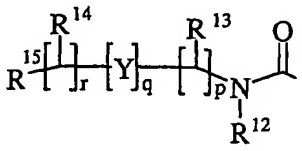
$R^7$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^7$ is optionally substituted by one or more substituents selected from $R^{18}$;

$R^8$ is hydrogen or $C_{1-4}$alkyl;

$R^9$ is hydrogen or $C_{1-4}$alkyl;

$R^{10}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{10}$ is optionally substituted by one or more substituents selected from $R^{19}$;

$R^{11}$ is carboxy, sulpho, sulphino, phosphono, -P(O)($OR^c$)($OR^d$), -P(O)(OH)($OR^c$), -P(O)(OH)($R^d$) or -P(O)($OR^c$)($R^d$) wherein $R^c$ and $R^d$ are independently selected from $C_{1-6}$alkyl; or $R^{11}$ is a group of formula (DIB):



(DIB)

wherein:

Y is –N($R^n$)-, -N($R^n$)C(O)-, -O-, and -S(O)a-; wherein a is 0-2 and $R^n$ is hydrogen or $C_{1-4}$alkyl;

$R^{12}$ is hydrogen or $C_{1-4}$alkyl;

$R^{13}$ and $R^{14}$ are independently selected from hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{13}$ and $R^{14}$ may be independently optionally substituted by one or more substituents selected from $R^{20}$;

$R^{15}$ is carboxy, sulpho, sulphino, phosphono, -P(O)($OR^e$)($OR^f$), -P(O)(OH)($OR^e$), -P(O)(OH)($R^e$) or -P(O)($OR^e$)($R^f$) wherein $R^e$ and $R^f$ are independently selected from $C_{1-6}$alkyl;

p is 1-3; wherein the values of $R^{13}$ may be the same or different;

q is 0-1;

r is 0-3; wherein the values of $R^{14}$ may be the same or different;

m is 0-2; wherein the values of $R^{10}$ may be the same or different;

n is 1-3; wherein the values of $R^7$ may be the same or different;

$R^{16}$, $R^{17}$ and $R^{18}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^{16}$, $R^{17}$ and $R^{18}$ may be independently optionally substituted on carbon by one or more $R^{21}$;

$R^{19}$ and $R^{20}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy,

$C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl, *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, sulpho, sulphino, amidino, phosphono, -P(O)(OR$^a$)(OR$^b$), -P(O)(OH)(OR$^a$), -P(O)(OH)(R$^a$) or -P(O)(OR$^a$)(R$^b$), wherein R$^a$ and R$^b$ are independently selected from $C_{1-6}$alkyl; wherein R$^{19}$ and R$^{20}$ may be independently optionally substituted on carbon by one or more R$^{22}$;

**R$^{21}$** and **R$^{22}$** are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor is selected from any one of Example 1-4 of WO 03/022830, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-4 are incorporated herein by reference. Claims 1-8 of WO 03/022830 are also incorporated herein by reference. A IBAT inhibitor selected from WO 03/022830 is any one of:

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{(R)-α-[*N*-(carboxymethyl)carbamoyl]benzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine

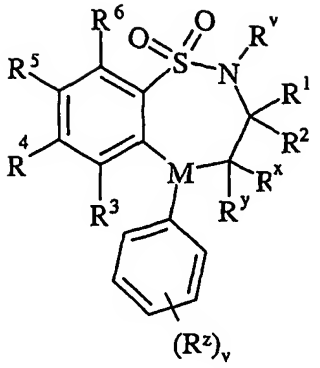
1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine ammonia salt

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{*N*-[α-(carboxy)-2-fluorobenzyl] carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine; and

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-{*N*-[1-(carboxy)-1-(thien-2-yl)methyl] carbamoylmethylthio}-2,3,4,5-tetrahydrobenzothiepine

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additional suitable IBAT inhibitors are those described in WO 03/022286. Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula (**EI**):



**(EI)**

wherein:

$\mathbf{R^v}$ is selected from hydrogen or $C_{1-6}$alkyl;

One of $\mathbf{R^1}$ and $\mathbf{R^2}$ are selected from hydrogen or $C_{1-6}$alkyl and the other is selected from $C_{1-6}$alkyl;

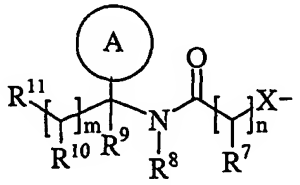
$\mathbf{R^x}$ and $\mathbf{R^y}$ are independently selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2;

**M** is selected from -N- or -CH-;

$\mathbf{R^z}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula **(EIA)**:



**(EIA)**

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl,

*N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^3$ and $R^6$ and the other of $R^4$ and $R^5$ may be optionally substituted on carbon by one or more $R^{16}$;

**X** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted by one or more substituents selected from $R^{17}$;

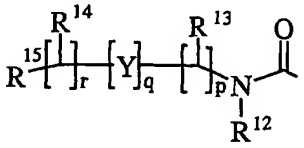
$\mathbf{R^7}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^7$ is optionally substituted by one or more substituents selected from $R^{18}$;

$\mathbf{R^8}$ is hydrogen or $C_{1-4}$alkyl;

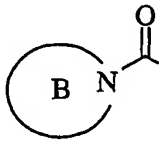
$\mathbf{R^9}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{10}}$ is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{10}$ is optionally substituted by one or more substituents selected from $R^{19}$;

$\mathbf{R^{11}}$ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR$^c$)(OR$^d$), -P(O)(OH)(OR$^c$), -P(O)(OH)(R$^d$) or -P(O)(OR$^c$)(R$^d$) wherein $R^c$ and $R^d$ are independently selected from $C_{1-6}$alkyl; or $R^{11}$ is a group of formula **(EIB)** or **(EIC)**:



**(EIB)**



**(EIC)**

wherein:

**Y** is –N($R^n$)-, -N($R^n$)C(O)-, -N($R^n$)C(O)(CR$^s$R$^t$)$_v$N($R^n$)C(O)-, -O-, and -S(O)a-; wherein a is 0-2, v is 1-2, $R^s$ and $R^t$ are independently selected from hydrogen or $C_{1-4}$alkyl optionally substituted by $R^{26}$ and $R^n$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{12}}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{13}}$ and $\mathbf{R^{14}}$ are independently selected from hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; and when q is 0, $R^{14}$ may additionally be selected from hydroxy; wherein $R^{13}$ and $R^{14}$ may be independently optionally substituted by one or more substituents selected from $R^{20}$;

$\mathbf{R^{15}}$ is carboxy, sulpho, sulphino, phosphono, -P(O)(OR$^e$)(OR$^f$), -P(O)(OH)(OR$^e$), -P(O)(OH)(R$^e$) or -P(O)(OR$^e$)(R$^f$) wherein $R^e$ and $R^f$ are independently selected from $C_{1-6}$alkyl;

**p** is 1-3; wherein the values of $R^{13}$ may be the same or different;

**q** is 0-1;

**r** is 0-3; wherein the values of $R^{14}$ may be the same or different;

**m** is 0-2; wherein the values of $R^{10}$ may be the same or different;

**n** is 1-3; wherein the values of $R^{7}$ may be the same or different;

**Ring B** is a nitrogen linked heterocyclyl substituted on carbon by one group selected from $R^{23}$, and optionally additionally substituted on carbon by one or more $R^{24}$; and wherein if said nitrogen linked heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by a group selected from $R^{25}$;

**$R^{16}$**, **$R^{17}$** and **$R^{18}$** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^{16}$, $R^{17}$ and $R^{18}$ may be independently optionally substituted on carbon by one or more $R^{21}$;

**$R^{19}$**, **$R^{20}$**, **$R^{24}$** and **$R^{26}$** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl, *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl, carbocyclyl, heterocyclyl, benzyloxycarbonylamino, sulpho, sulphino, amidino, phosphono, -P(O)(OR$^a$)(OR$^b$), -P(O)(OH)(OR$^a$), -P(O)(OH)(R$^a$) or -P(O)(OR$^a$)(R$^b$), wherein R$^a$ and R$^b$ are independently selected from $C_{1-6}$alkyl; wherein $R^{19}$, $R^{20}$, $R^{24}$ and $R^{26}$ may be independently optionally substituted on carbon by one or more $R^{22}$;

**$R^{21}$** and **$R^{22}$** are independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl;

**$R^{23}$** is carboxy, sulpho, sulphino, phosphono, -P(O)(OR$^g$)(OR$^h$), -P(O)(OH)(OR$^g$), -P(O)(OH)(R$^g$) or -P(O)(OR$^g$)(R$^h$) wherein R$^g$ and R$^h$ are independently selected from $C_{1-6}$alkyl;

$R^{25}$ is selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A particular IBAT inhibitor is selected from any one of Example 1-39 of WO 03/022286, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and the compounds of Examples 1-39 are incorporated herein by reference. Claims 1-10 of WO 03/022286 are also incorporated herein by reference. A IBAT inhibitor selected from WO 03/022286 is any one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

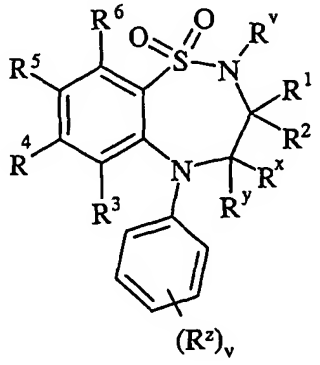
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Further suitable compounds possessing IBAT inhibitory activity have the following structure of formula **(FFI)**:



**(FI)**

wherein:

$\mathbf{R^v}$ is selected from hydrogen or $C_{1-6}$alkyl;

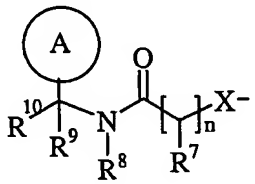
One of $\mathbf{R^1}$ and $\mathbf{R^2}$ are selected from hydrogen or $C_{1-6}$alkyl and the other is selected from $C_{1-6}$alkyl;

$\mathbf{R^x}$ and $\mathbf{R^y}$ are independently selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, *N*-($C_{1-6}$alkyl)amino, *N*,*N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2;

$\mathbf{R^z}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

v is 0-5;

one of $\mathbf{R^4}$ and $\mathbf{R^5}$ is a group of formula **(FIA)**:




**(FIA)**

$\mathbf{R^3}$ and $\mathbf{R^6}$ and the other of $\mathbf{R^4}$ and $\mathbf{R^5}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl; wherein $R^3$ and $R^6$ and the other of $R^4$ and $R^5$ may be optionally substituted on carbon by one or more $R^{17}$;

**X** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

**Ring A** is aryl or heteroaryl; wherein Ring A is optionally substituted on carbon by one or more substituents selected from $R^{18}$;

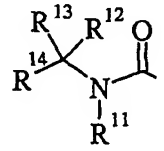
$\mathbf{R^7}$ is hydrogen, $C_{1-6}$alkyl, carbocyclyl or heterocyclyl; wherein $R^7$ is optionally substituted on carbon by one or more substituents selected from $R^{19}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{20}$;

$\mathbf{R^8}$ is hydrogen or $C_{1-6}$alkyl;

$\mathbf{R^9}$ is hydrogen or $C_{1-6}$alkyl;

$\mathbf{R^{10}}$ is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl,

*N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclyl, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_p$-$R^{21}$-($C_{1-10}$alkylene)$_q$- or heterocyclyl-($C_{1-10}$alkylene)$_r$-$R^{22}$-($C_{1-10}$alkylene)$_s$-; wherein $R^{10}$ is optionally substituted on carbon by one or more substituents selected from $R^{23}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{24}$; or $R^{10}$ is a group of formula (**FIB**):



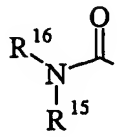
**(FIB)**

wherein:

**$R^{11}$** is hydrogen or $C_{1-6}$alkyl;

**$R^{12}$** and **$R^{13}$** are independently selected from hydrogen, halo, carbamoyl, sulphamoyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkanoyl, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, carbocyclyl or heterocyclyl; wherein $R^{12}$ and $R^{13}$ may be independently optionally substituted on carbon by one or more substituents selected from $R^{25}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{26}$;

**$R^{14}$** is selected from hydrogen, halo, carbamoyl, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkanoyl, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclyl, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_p$-$R^{27}$-($C_{1-10}$alkylene)$_q$- or heterocyclyl-($C_{1-10}$alkylene)$_r$-$R^{28}$-($C_{1-10}$alkylene)$_s$-; wherein $R^{14}$ may be optionally substituted on carbon by one or more substituents selected from $R^{29}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{30}$; or $R^{14}$ is a group of formula (**FIC**):



(FIC)

$R^{15}$ is hydrogen or $C_{1-6}$alkyl;

$R^{16}$ is hydrogen or $C_{1-6}$alkyl; wherein $R^{16}$ may be optionally substituted on carbon by one or more groups selected from $R^{31}$;

**n** is 1-3; wherein the values of $R^7$ may be the same or different;

$R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ or $R^{31}$ are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclyl, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_p$-$R^{32}$-($C_{1-10}$alkylene)$_q$- or heterocyclyl-($C_{1-10}$alkylene)$_r$-$R^{33}$-($C_{1-10}$alkylene)$_s$-; wherein $R^{17}$, $R^{18}$, $R^{19}$, $R^{23}$, $R^{25}$, $R^{29}$ or $R^{31}$ may be independently optionally substituted on carbon by one or more $R^{34}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{35}$;

$R^{21}$, $R^{22}$, $R^{27}$, $R^{28}$, $R^{32}$ or $R^{33}$ are independently selected from -O-, -$NR^{36}$-, -$S(O)_x$-, -$NR^{36}C(O)NR^{36}$-, -$NR^{36}C(S)NR^{36}$-, -OC(O)N=C-, -$NR^{36}C(O)$- or -$C(O)NR^{36}$-; wherein $R^{36}$ is selected from hydrogen or $C_{1-6}$alkyl, and x is 0-2;

**p**, **q**, **r** and **s** are independently selected from 0-2;

$R^{34}$ is selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl, *N,N*-dimethylsulphamoyl, *N*-methylsulphamoylamino and *N,N*-dimethylsulphamoylamino;

$R^{20}$, $R^{24}$, $R^{26}$, $R^{30}$ or $R^{35}$ are independently selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl; or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Suitable IBAT inhibitors having the above structure are selected from any one of:

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine (both enantiomers);

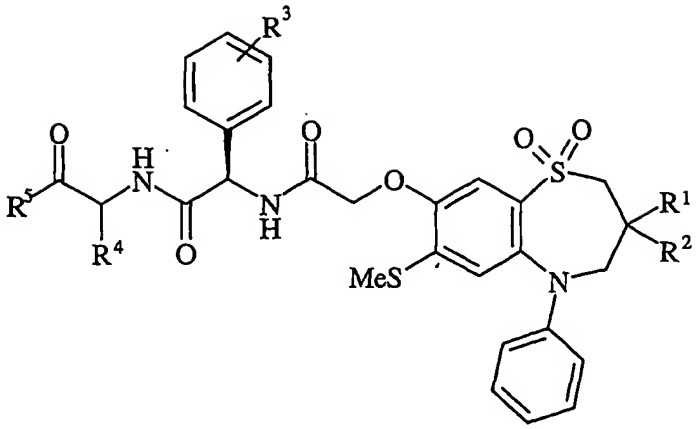
1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N*-{2-(S)-[*N*-(carbamoylmethyl)carbamoyl]pyrrolidin-1-ylcarbonylmethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-{*N*-[2-(3,4,5-trihydroxyphenyl)ethyl]carbamoyl}benzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; or

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(R)-3-(S)-4-(S)-5-(R)-3,4,5,6-tetrahydroxytetrahydropyran-2-ylmethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Further suitable IBAT inhibitors include a compound of formula **(GI)**:



(GI)

wherein:

$R^1$ and $R^2$ are independently selected from $C_{1-4}$alkyl;

$R^3$ is hydrogen, hydroxy or halo;

$R^4$ is $C_{1-4}$alkyl optionally substituted by hydroxy, methoxy and methylS(O)a wherein a is 0-2

$R^5$ is hydroxy or HOC(O)CH($R^6$)NH-;

$R^6$ is selected from hydrogen and $C_{1-3}$alkyl optionally substituted by hydroxy, methoxy and methylS(O)a wherein a is 0-2;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; with the proviso that when $R^1$ and $R^2$ are both butyl, $R^5$ is hydroxy and $R^4$ is methylthiomethyl, methylsulphinylmethyl, 2-methylthioethyl, hydroxymethyl, methoxymethyl; $R^3$ is not hydrogen; and with the proviso that when $R^1$ and $R^2$ are both butyl, $R^5$ is HOC(O)CH($R^6$)NH-, $R^6$ is hydroxymethyl and $R^4$ is hydroxymethyl; $R^3$ is not hydrogen.

Suitable IBAT inhibitors having the above structure are selected from any one of:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxybutyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-

methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylbutyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-mesylethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylbutyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-

benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylthioethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methylsulphinylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-mesylethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-2-methoxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylthiopropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-methylsulphonylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxy-3-mesylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

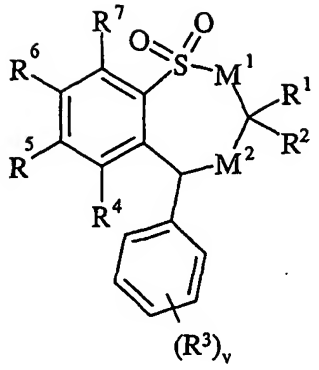
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additional suitable IBAT inhibitors having the above structure are selected from:

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; or

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(*R*)-α-[*N'*-((*S*)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine.

Further suitable IBAT inhibitors are those having the structure (**HI**):



(HI)

wherein

$M^1$ is $-CH_2-$ or $-NR^{21}-$;

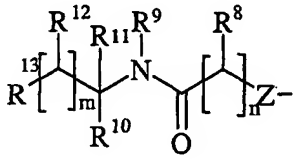
$M^2$ is $-CR^{22}R^{23}-$ or $-NR^{24}-$; provided that if $M^1$ is $-NR^{21}-$, $M^2$ is $-CR^{22}R^{23}-$;

One of $R^1$ and $R^2$ are selected from hydrogen, $C_{1-6}$alkyl or $C_{2-6}$alkenyl and the other is selected from $C_{1-6}$alkyl or $C_{2-6}$alkenyl;

$R^3$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkyl$S(O)_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl and *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl;

v is 0-5;

one of $R^5$ and $R^6$ is a group of formula (HIA):



(HIA)

$R^4$ and $R^7$ and the other of $R^5$ and $R^6$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkyl$S(O)_a$ wherein a is 0 to 2, $C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^4$ and $R^7$ and the other of $R^5$ and $R^6$ may be optionally substituted on carbon by one or more $R^{25}$;

**Z** is -O-, -N($R^a$)-, -S(O)$_b$- or -CH($R^a$)-; wherein $R^a$ is hydrogen or $C_{1-6}$alkyl and b is 0-2;

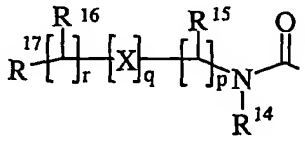
**$R^8$** is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^8$ may be optionally substituted on carbon by one or more substituents selected from $R^{26}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{27}$;

**$R^9$** is hydrogen or $C_{1-4}$alkyl;

**$R^{10}$** and **$R^{11}$** are independently selected from hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; or $R^{10}$ and $R^{11}$ together form $C_{2-6}$alkylene; wherein $R^{10}$ and $R^{11}$ or $R^{10}$ and $R^{11}$ together may be independently optionally substituted on carbon by one or more substituents selected from $R^{28}$; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more $R^{29}$;

**$R^{12}$** is hydrogen, $C_{1-4}$alkyl, carbocyclyl or heterocyclyl; wherein $R^{12}$ may be optionally substituted on carbon by one or more substituents selected from $R^{30}$; and wherein if said heterocyclyl contains an -NH- moiety, that nitrogen may be optionally substituted by one or more $R^{31}$;

**$R^{13}$** is hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkoxycarbonyl, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclic group, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_e$-$R^{32}$-($C_{1-10}$alkylene)$_f$- or heterocyclyl-($C_{1-10}$alkylene)$_g$-$R^{33}$-($C_{1-10}$alkylene)$_h$-; wherein $R^{13}$ may be optionally substituted on carbon by one or more substituents selected from $R^{36}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{37}$; or $R^{13}$ is a group of formula **(HIB)**:



**(HIB)**

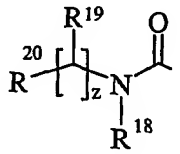
wherein:

**X** is $-N(R^{38})-$, $-N(R^{38})C(O)-$, -O-, and $-S(O)_a-$; wherein a is 0-2 and $R^{38}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{14}}$ is hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{15}}$ and $\mathbf{R^{16}}$ are independently selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl, $C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, carbocyclyl or heterocyclic group; wherein $R^{15}$ and $R^{16}$ may be independently optionally substituted on carbon by one or more substituents selected from $R^{41}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{42}$;

$\mathbf{R^{17}}$ is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, $C_{1-10}$alkoxycarbonyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclic group, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_e$-$R^{43}$-($C_{1-10}$alkylene)$_f$- or heterocyclyl-($C_{1-10}$alkylene)$_g$-$R^{44}$-($C_{1-10}$alkylene)$_h$-; wherein $R^{17}$ may be optionally substituted on carbon by one or more substituents selected from $R^{47}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{48}$; or $R^{17}$ is a group of formula **(HIC)**:



**(HIC)**

wherein:

$\mathbf{R^{18}}$ is selected from hydrogen or $C_{1-4}$alkyl;

$\mathbf{R^{19}}$ is selected from hydrogen, halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, $C_{1-6}$alkyl, $C_{2-6}$alkenyl, $C_{2-6}$alkynyl, $C_{1-6}$alkoxy, $C_{1-6}$alkanoyl,

$C_{1-6}$alkanoyloxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkanoylamino, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2, $C_{1-6}$alkoxycarbonyl, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, carbocyclyl or heterocyclic group; where $R^{19}$ may be independently optionally substituted on carbon by one or more substituents selected from $R^{51}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{52}$;

$R^{20}$ is selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkoxycarbonyl, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkylS(O)$_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclic group, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_e$-$R^{53}$-($C_{1-10}$alkylene)$_f$- or heterocyclyl-($C_{1-10}$alkylene)$_g$-$R^{54}$-($C_{1-10}$alkylene)$_h$-; wherein $R^{20}$ may be independently optionally substituted on carbon by one or more $R^{57}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{58}$;

**p** is 1-3; wherein the values of $R^{15}$ may be the same or different;

**q** is 0-1;

**r** is 0-3; wherein the values of $R^{16}$ may be the same or different;

**m** is 0-2; wherein the values of $R^{12}$ may be the same or different;

**n** is 1-2; wherein the values of $R^{8}$ may be the same or different;

**z** is 0-3; wherein the values of $R^{19}$ may be the same or different;

$R^{21}$ is selected from hydrogen or $C_{1-6}$alkyl;

$R^{22}$ and $R^{23}$ are independently selected from hydrogen, hydroxy, amino, mercapto, $C_{1-6}$alkyl, $C_{1-6}$alkoxy, *N*-($C_{1-6}$alkyl)amino, *N,N*-($C_{1-6}$alkyl)$_2$amino, $C_{1-6}$alkylS(O)$_a$ wherein a is 0 to 2;

$R^{24}$ is selected from hydrogen, hydroxy, $C_{1-6}$alkyl, $C_{1-4}$alkoxy and $C_{1-6}$alkanoyloxy;

$R^{25}$ is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, $C_{1-4}$alkanoyloxy, *N*-($C_{1-4}$alkyl)amino, *N,N*-($C_{1-4}$alkyl)$_2$amino, $C_{1-4}$alkanoylamino, *N*-($C_{1-4}$alkyl)carbamoyl, *N,N*-($C_{1-4}$alkyl)$_2$carbamoyl, $C_{1-4}$alkylS(O)$_a$ wherein a is 0 to 2,

$C_{1-4}$alkoxycarbonyl, *N*-($C_{1-4}$alkyl)sulphamoyl and *N,N*-($C_{1-4}$alkyl)$_2$sulphamoyl; wherein $R^{25}$, may be independently optionally substituted on carbon by one or more $R^{67}$;

**$R^{26}$, $R^{28}$, $R^{30}$, $R^{36}$, $R^{41}$, $R^{47}$, $R^{51}$** and **$R^{57}$** are independently selected from halo, nitro, cyano, hydroxy, amino, carbamoyl, mercapto, sulphamoyl, hydroxyaminocarbonyl, $C_{1-10}$alkyl, $C_{2-10}$alkenyl, $C_{2-10}$alkynyl, $C_{1-10}$alkoxy, $C_{1-10}$alkanoyl, $C_{1-10}$alkanoyloxy, $C_{1-10}$alkoxycarbonyl, *N*-($C_{1-10}$alkyl)amino, *N,N*-($C_{1-10}$alkyl)$_2$amino, *N,N,N*-($C_{1-10}$alkyl)$_3$ammonio, $C_{1-10}$alkanoylamino, *N*-($C_{1-10}$alkyl)carbamoyl, *N,N*-($C_{1-10}$alkyl)$_2$carbamoyl, $C_{1-10}$alkyl$S(O)_a$ wherein a is 0 to 2, *N*-($C_{1-10}$alkyl)sulphamoyl, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoyl, *N*-($C_{1-10}$alkyl)sulphamoylamino, *N,N*-($C_{1-10}$alkyl)$_2$sulphamoylamino, $C_{1-10}$alkoxycarbonylamino, carbocyclyl, carbocyclyl$C_{1-10}$alkyl, heterocyclic group, heterocyclyl$C_{1-10}$alkyl, carbocyclyl-($C_{1-10}$alkylene)$_e$-$R^{59}$-($C_{1-10}$alkylene)$_f$- or heterocyclyl-($C_{1-10}$alkylene)$_g$-$R^{60}$-($C_{1-10}$alkylene)$_h$-; wherein $R^{26}$, $R^{28}$, $R^{30}$, $R^{36}$, $R^{41}$, $R^{47}$, $R^{51}$ and $R^{57}$ may be independently optionally substituted on carbon by one or more $R^{63}$; and wherein if said heterocyclyl contains an -NH- group, that nitrogen may be optionally substituted by a group selected from $R^{64}$;

**$R^{27}$, $R^{29}$, $R^{31}$, $R^{37}$, $R^{42}$, $R^{48}$, $R^{52}$, $R^{58}$** and **$R^{64}$** are independently selected from $C_{1-6}$alkyl, $C_{1-6}$alkanoyl, $C_{1-6}$alkylsulphonyl, sulphamoyl, *N*-($C_{1-6}$alkyl)sulphamoyl, *N,N*-($C_{1-6}$alkyl)$_2$sulphamoyl, $C_{1-6}$alkoxycarbonyl, carbamoyl, *N*-($C_{1-6}$alkyl)carbamoyl, *N,N*-($C_{1-6}$alkyl)$_2$carbamoyl, benzyl, phenethyl, benzoyl, phenylsulphonyl and phenyl;

**$R^{32}$, $R^{33}$, $R^{43}$, $R^{44}$, $R^{53}$, $R^{54}$, $R^{59}$** and **$R^{60}$**are independently selected from -O-, -$NR^{65}$-, -$S(O)_x$-, -$NR^{65}C(O)NR^{66}$-, -$NR^{65}C(S)NR^{66}$-, -OC(O)N=C-, -$NR^{65}C(O)$- or -$C(O)NR^{65}$-; wherein $R^{65}$ and $R^{66}$ are independently selected from hydrogen or $C_{1-6}$alkyl, and x is 0-2;

**$R^{63}$** and **$R^{67}$** re independently selected from halo, hydroxy, cyano, carbamoyl, ureido, amino, nitro, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, methyl, ethyl, methoxy, ethoxy, vinyl, allyl, ethynyl, methoxycarbonyl, formyl, acetyl, formamido, acetylamino, acetoxy, methylamino, dimethylamino, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, methylthio, methylsulphinyl, mesyl, *N*-methylsulphamoyl and *N,N*-dimethylsulphamoyl; and

**e**, **f**, **g** and **h** are independently selected from 0-2;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Additional suitable IBAT inhibitors having the above structure are selected from any one of:

(+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

(+/-)-trans-1,1-dioxo-3-ethyl-3-butyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,4-benzothiazepine;

1,1-dioxo-3-ethyl-3-butyl-4-hydroxy-5-phenyl-7-(*N*-{α-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-2-fluorobenzyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiapine; or

1,1-dioxo-3-butyl-3-ethyl-4-hydroxy-5-phenyl-7-(*N*-{1-[*N*'-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-1-(cyclohexyl)methyl}carbamoylmethylthio)-2,3,4,5-tetrahydrobenzothiepine.

Compounds of formula **(AI)**, **(BI)**, **(CI)**, **(DI)**, **(EI)**, **(FI)**, **(GI)** and **(HI)** or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof may be prepared by processes known in the art.

In a particular aspect of the invention an IBAT inhibitor or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof is an IBAT inhibitor or a pharmaceutically acceptable salt thereof.

Suitable pharmaceutically acceptable salts of the above compounds, or other compounds disclosed herein, are, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, acetate or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The IBAT inhibitor compounds disclosed herein may be administered in the form of a pro-drug which is broken down in the human or animal body to give the parent compound. Examples of pro-drugs include *in vivo* hydrolysable esters and *in vivo* hydrolysable amides.

An *in vivo* hydrolysable ester of a compound containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal

body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include $C_{1-6}$alkoxymethyl esters for example methoxymethyl, $C_{1-6}$alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, $C_{3-8}$cycloalkoxycarbonyloxy$C_{1-6}$alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and $C_{1-6}$alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds.

An *in vivo* hydrolysable ester of a compound containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

A suitable value for an *in vivo* hydrolysable amide of a compound containing a carboxy group is, for example, a *N*-$C_{1-6}$alkyl or *N,N*-di-$C_{1-6}$alkyl amide such as *N*-methyl, *N*-ethyl, *N*-propyl, *N,N*-dimethyl, *N*-ethyl-*N*-methyl or *N,N*-diethyl amide.

**Experimental**

The following four *in vitro* examples (Examples A-D) illustrate how calcium salts may be used for lowering the bile salt concentrations in aqueous solutions. These experiments illustrate the underlying mechanism for bile acid sequestering *in vivo*.

Example A Reduction of the concentration of taurocholic acid in simulated intestinal fluid caused by addition of calcium chloride

A solution simulating the human intestinal fluid in the fasted state, FaSSIF, was prepared by dissolving the following components in deionised water:

| | | |
|---|---|---|
| Sodium taurocholate | 3.1 | mM |
| E-phosphatidylcholine | 0.75 | mM |
| Sodium phosphate | 28.7 | mM |
| Sodium chloride | 105.8 | mM |

The pH was adjusted to 6.5.

A separate solution of calcium chloride was prepared by dissolving 149.2 mM of the salt in deionised water.

5.0 ml of FaSSIF was added to each of 7 glass vials. A known volume, varying from 0 to 0.5 ml, of the calcium chloride solution was added to each vial. Each sample was inspected visually immediately after the calcium chloride addition.

A volume of 1.0 ml was withdrawn from each sample and centrifuged for 20 mins at 14 000 rpm. The clear supernatant of each sample was collected and analysed with respect to bile acid content. The analyses were carried out using a bile acid analysis kit which employs an enzymatic colour reaction. The concentration of bile acid is proportional to the colour intensity which is determined by spectrophotometry.

*Table A. The effect of calcium chloride addition to FaSSIF on the taurocholate concentration as reflected in the sample absorbance after the enzymatic colour reaction.*

| Sample | Added amount of calcium chloride (μmol) | Absorbance |
|---|---|---|
| A | 0 | 0.0943 |
| B | 7.5 | 0.0933 |
| C | 14.9 | 0.0890 |
| D | 22.4 | 0.0843 |
| E | 29.8 | 0.0783 |
| F | 44.8 | 0.0735 |
| G | 74.6 | 0.0718 |

**Table A**

A precipitate was formed in all samples immediately after calcium chloride was added. Furthermore, the amount of precipitation appeared to increase with increasing added volume of the calcium chloride solution. The bile acid analyses shows that the concentration of taurocholate in the aqueous solution decreased with increasing added amount of calcium chloride.

Example B Reduction of the concentration of bile acids in aqueous solution caused by addition of calcium chloride

A solution containing a mixture of bile acids was prepared by dissolving the following components in deionised water:

| | | |
|---|---|---|
| Sodium lithocholate | 0.27 | mM |
| Sodium deoxycholate | 2.2 | mM |
| Sodium ursodeoxycholate | 0.34 | mM |
| Sodium cholate | 0.24 | mM |
| E-phosphatidylcholine | 0.74 | mM |
| TES buffer | 30.3 | mM |
| Sodium chloride | 100.1 | mM |

The pH was adjusted to 7.4.

A calcium chloride solution was prepared by dissolving the following components in deionised water:

| | | |
|---|---|---|
| Calcium chloride | 200.2 | mM |
| TES buffer | 30.3 | mM |
| Sodium chloride | 100.1 | mM |

The pH was adjusted to 7.4.

2.0 ml of the bile acid solution was added to each of 6 glass vials. A known volume, varying from 0 to 300 µl, of the calcium chloride solution was added to each vial. Each sample was inspected visually immediately after the calcium chloride addition. 1.5 ml of each sample was transferred into a centrifugation tube and centrifuged for 20 mins at 14 000 rpm. The clear supernatant was collected and analysed with respect to bile acid content. The analyses were carried out using a bile acid analysis kit which employs an enzymatic colour reaction. The concentration of bile acid is proportional to the colour intensity which is determined by spectrophotometry.

*Table B. The effect of addition of calcium chloride on the bile acid concentration.*

| Sample | Added amount of calcium chloride (µmol) | Concentration of bile acids (mM) |
|---|---|---|
| A | 0 | 2.9 |
| B | 3.0 | 2.2 |
| C | 6.0 | 2.1 |
| D | 12.0 | 1.9 |
| E | 30.0 | 0.8 |
| F | 60.1 | 0.7 |

**Table B**

Again, a precipitate was formed in all samples immediately after calcium chloride was added. Furthermore, the amount of precipitation appeared to increase with increasing added amount of calcium chloride. The bile acid analyses shows that the concentration of bile acids in the aqueous solution decreased with increasing added amount of calcium chloride.

Example C Reduction of the concentration of sodium glycodeoxycholate (GDC) in aqueous solution caused by addition of calcium phosphate

A stock solution of sodium glycodeoxycholate (GDC) was prepared by dissolving the following substances in deionised water:

| | | |
|---|---|---|
| Sodium glycodeoxycholate (GDC) | 15.0 | mM |
| Sodium phosphate | 28.9 | mM |
| Sodium chloride | 106 | mM |

The pH was adjusted to 7.4 with sodium hydroxide.

A similar buffer solution with the same content, except for the bile acid was also prepared.

200 mg calcium phosphate (crystalline) was weighed into each of 10 glass vials labelled A – J. The GDC stock solution and the buffer solution were added in various proportions to the samples so that the total solution volume in each sample was 10 ml. The resulting initial GDC concentrations in the samples were 1 – 15 mM. The samples were equilibrated for several hours. The solid material in the samples were removed by centrifugation and/or filtration, and the obtained clear supernatants were analysed with respect to GDC content. The analyses were carried out by HPLC.

*Figure C. Reduction of glycodeoxycholate (GDC) concentration in aqueous solutions caused by the addition of calcium phosphate.*

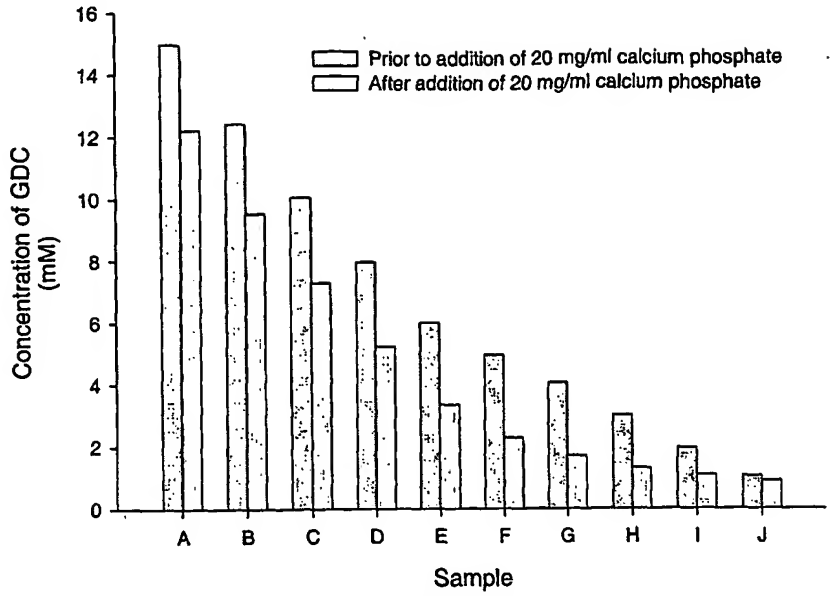



**Figure C**

The results of the analyses show that the GDC concentration had been reduced by the presence of calcium phosphate in all samples.

Example D Reduction of the concentration of sodium deoxycholate (DC) in aqueous solution caused by addition of calcium phosphate

A stock solution of sodium deoxycholate (DC) was prepared by dissolving the following substances in deionised water:

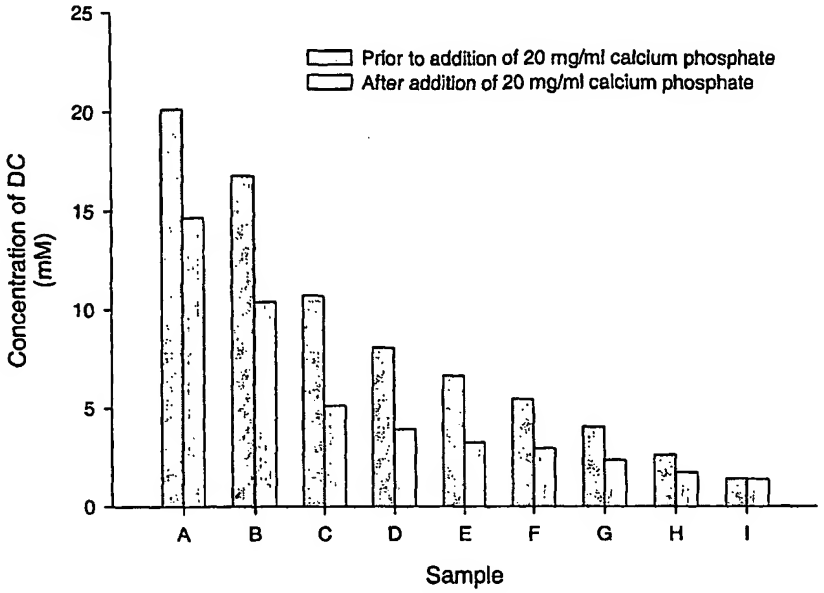
| | | |
|---|---|---|
| Sodium glycodeoxycholate (DC) | 20.1 | mM |
| Sodium phosphate | 28.9 | mM |
| Sodium chloride | 106 | mM |

The pH was adjusted to 7.4 with sodium hydroxide.

A similar buffer solution with the same content, except for the bile acid was also prepared.

200 mg calcium phosphate (crystalline) was weighed into each of 9 glass vials labelled A – I. The DC stock solution and the buffer solution were added in various proportions to the samples so that the total solution volume in each sample was 10 ml. The resulting initial DC concentrations in the samples were 1 – 20 mM. The samples were equilibrated for several hours. The solid material in the samples were removed by centrifugation and/or filtration, and the obtained clear supernatants were analysed with respect to DC content. The analyses were carried out by HPLC.

*Figure D.* *Reduction of deoxycholate (DC) concentration in aqueous solutions caused by the addition of calcium phosphate.*




The results of the analyses clearly showed that the DC concentration had been reduced by the presence of calcium phosphate in all samples.

Colon fistulated dogs may be used to demonstrate the effectiveness of the combination of the present invention in preventing diarrhoea. The IBAT inhibitor is dosed orally at a dose that will cause diarrhoea, for example 25-50μmol/kg. The metal salt is then introduced into the colon, through the fistulae, to see if the diarrhoea can be prevented. The dose of the metal salt varies and can be determined after analysing the bile acid concentration in faeces from dogs having been exposed to the same dose of the IBAT inhibitor. The following example (Examples E) illustrates how to measure the lowering effect of a metal salt of the bile acid concentration *in vivo*.

Example E *In vivo* reduction of the bile acid concentration in the feacal aqueous phase of the dog treated with an IBAT inhibitor by intracolonic administration of calcium chloride

Labrador dogs with a colon fistula were used for studying the effect of intracolonic administration of an aqueous calcium chloride solution on the bile acid content in faecal water of dogs treated with an IBAT inhibitor.

A solution of an IBAT inhibitor was administered directly into the stomach of the dog via an orogastric tube (t = 0 hours). The dog was fed 30 minutes after the administration of

the IBAT inhibitor (t = 0.5 hours). The calcium chloride solution was administered 60 minutes after the IBAT inhibitor dosing (t = 1 hour).

Faeces was collected during the first 8 hours after administration, and the time for each bowel movement was recorded. Each faeces sample was homogenized with a high-shear mixer and, subsequently, centrifuged in order to separate the solid material from the faecal water phase. The faecal water was collected and analysed with respect to bile acid content. The amount of bile acid in the faecal water was related to the amount of solid material in each faeces sample.

*Figure E. Bile acid concentrations in the faecal water of dog treated with an IBAT inhibitor after intracolonic administration of calcium chloride.*

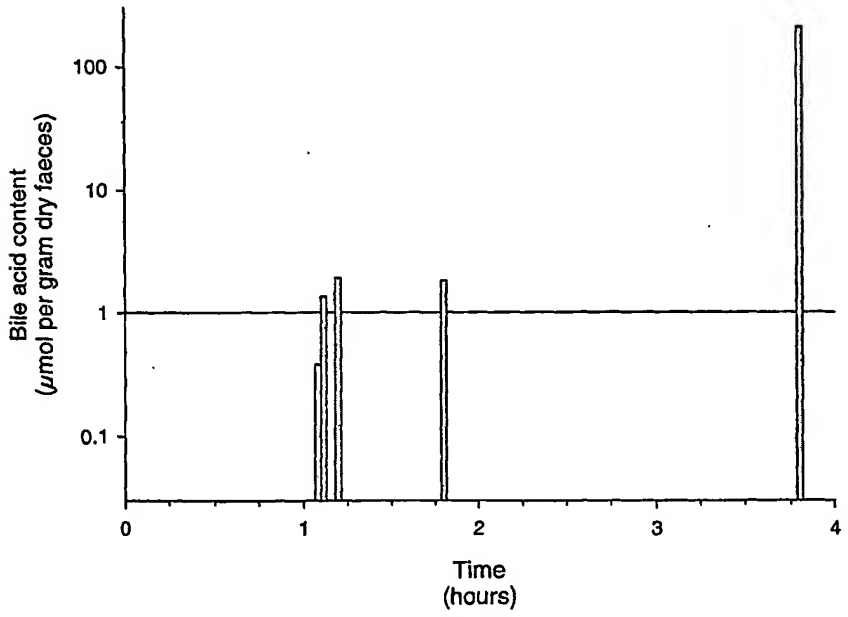



**Figure E**

The results show that as long as calcium chloride is present in the colon, the bile acid concentration is relatively constant. After approximately 3.5 hours most of the calcium chloride has been removed from the colon, either by absorption or by the bowel movements. At this point, the IBAT inhibitor is still active at its site of action and the flow of bile acids into the colon is still substantial. The absence of calcium chloride in the colon allows for high bile acid concentration in the faecal output.

According to another feature of the invention there is provided the use of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon,

for the prevention of diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to another feature of the invention there is provided the use of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in the manufacture of a medicament for the prevention of diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

A method of preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, which comprises administering to a patient in need thereof, a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

According to another feature of the invention there is provided the use of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

Suitably the production of an IBAT inhibitory effect means the treatment of hyperlipidaemic conditions. Suitably the production of an IBAT inhibitory effect means the treatment of dyslipidemic conditions and disorders such as hyperlipidaemia, hypertrigliceridemia, hyperbetalipoproteinemia (high LDL), hyperprebetalipoproteinemia (high VLDL), hyperchylomicronemia, hypolipoproteinemia, hypercholesterolemia, hyperlipoproteinemia and hypoalphalipoproteinemia (low HDL). Suitably the production of an IBAT inhibitory effect means the treatment of different clinical conditions such as atherosclerosis, arteriosclerosis, arrhythmia, hyper-thrombotic conditions, vascular dysfunction, endothelial dysfunction, heart failure, coronary heart diseases, cardiovascular diseases, myocardial infarction, angina pectoris, peripheral vascular diseases, inflammation of cardiovascular tissues such as heart, valves, vasculature, arteries and veins, aneurisms, stenosis, restenosis, vascular plaques, vascular fatty streaks, leukocytes, monocytes and/or macrophage infiltration, intimal thickening, medial thinning, infectious and surgical trauma and vascular thrombosis, stroke and transient ischaemic attacks. Suitably the production of an IBAT inhibitory effect means the treatment of atherosclerosis, coronary heart diseases,

myocardial infarction, angina pectoris, peripheral vascular diseases, stroke and transient ischaemic attacks.

According to another feature of the invention there is provided the use of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in the manufacture of a medicament for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, which medicament comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

Therefore according to the present invention, there is provided a method of preventing diarrhoea that would result from excess bile acids in the intestine following administration of an effective amount an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal said effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in

association with a pharmaceutically acceptable diluent or carrier for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in association with a pharmaceutically acceptable diluent or carrier; for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a warm-blooded animal, such as man.

The pharmaceutical compositions may be in a form suitable for oral administration, for example as a tablet or capsule. In general the above compositions may be prepared in a conventional manner using conventional excipients.

According to an additional feature of the invention, there is provided an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, for use as a medicament.

According to an additional feature of the invention, there is provided an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

According to an additional feature of the invention, there is provided an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a kit comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, optionally with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, optionally with instructions for use; for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a kit comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon; optionally with instructions for use; for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a kit comprising:

a) an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon; in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use.

According to a further aspect of the present invention there is provided a kit comprising:

a) an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon; in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use;

for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a kit comprising:

a) an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;

b) a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon; in a second unit dosage form; and

c) container means for containing said first and second dosage forms; and optionally

d) with instructions for use;

for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination comprising an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, optionally together with a pharmaceutically acceptable diluent or carrier; to a warm-blooded animal, such as man in need of such therapeutic treatment.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, optionally together with a pharmaceutically

acceptable diluent or carrier for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, in combination with an effective amount of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, optionally together with a pharmaceutically acceptable diluent or carrier; for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm-blooded animal, such as man.

The IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.01-50 mg/kg, and this would be expected to provide a therapeutically-effective dose. A unit dose from such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. In one aspect of the invention a daily dose in the range of 0.02-50 mg/kg is employed. In another aspect a daily dose in the rage of 0.02-20 mg/kg is employed. In another aspect of the invention the compound of formula (I), or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.001- 20 mg /kg or 0.1 - 200 mg /day, particularly 1 -20 mg/day to provide a therapeutically-effective dose. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The metal salt will normally be administered to a warm-blooded animal at a unit dose which will be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient. Suitably this dose will be 2g or less per patient per day. Suitably this dose will be 1g or less per patient per day. More suitably it will be 500mg or less per patient per day. In another aspect a daily dose in the range of 50-100 mg per day is employed.

The dosage of each of the two drugs and their proportions have to be composed so that the best possible treatment effects, as defined by national and international guidelines (which are periodically reviewed and re-defined), will be met.

For the avoidance of doubt, where the prevention of diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof is referred to, it is to be understood that this also refers to the treatment of diarrhoea that has resulted from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

The combination therapy defined hereinbefore may also involve, in addition to the combination, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

Suitable additional substances include HMG Co-A reductase inhibitors, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable HMG Co-A reductase inhibitors, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are statins well known in the art. Particular statins are fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin, dalvastatin, mevastatin and rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A further particular statin is rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A preferable particular statin is rosuvastatin calcium salt.

Further suitable additional substances include:

- a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;
- a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;
- a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

- a fibric acid derivative; for example clofibrate, gemfibrozil, fenofibrate, ciprofibrate and bezafibrate;
- a nicotinic acid derivative, for example, nicotinic acid (niacin), acipimox and niceritrol;
- a phytosterol compound for example stanols;
- probucol;
- an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);
- an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, a diuretic or a vasodilator;
- insulin;
- sulphonylureas including glibenclamide, tolbutamide;
- metformin; and/or
- acarbose;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used as an additional substance include but are not limited to, the following compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present

invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use as an additional substance, include but are not limited to candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Additional suitable additional substances are PPAR alpha and/or gamma agonists, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma agonist refers to WY-14643, clofibrate, fenofibrate, bezafibrate, GW 9578, troglitazone, pioglitazone, rosiglitazone, eglitazone, proglitazone, BRL-49634, KRP-297, JTT-501, SB 213068, GW 1929, GW 7845, GW 0207, L-796449, L-165041 and GW 2433. Particularly a PPAR alpha and/or gamma agonist refers to (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl] propanoic acid and pharmaceutically acceptable salts thereof.

Therefore in a further aspect of the invention there is provided a combination which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, and one or more suitable additional substances as defined herein above.

According to another feature of the invention there is provided the use of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, and one or more suitable additional substances as defined herein above in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, and one or more suitable additional substances as defined herein above, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

According to a further feature of this aspect of the invention there is provided a method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, and one or more suitable additional substances as defined herein above.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, and one or more suitable additional substances as defined herein above, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in combination with a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, and one or more suitable additional substances as defined herein above, in association with a pharmaceutically acceptable diluent or carrier for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

The metal salt can be formulated in a delayed release single or multiple unit oral formulation. The delayed release of the metal salt can be achieved by for example using techniques producing formulations with time dependent or pH dependent release or enzymatically degradable formulations (Pharmaceutics. The Science of Dosage Form Design Second Edition; Ed. Micheal E Aulton; Harcourt Publishers Limited; 2002). These formulations can be manufactured with conventional techniques, for example as described in Aulton,(see above), or Industrial Aspects of Pharmaceutics, Ed Erik Sandell; Swedish

Pharmaceutical Press; 1993). Another reference illustrating how substances can be formulated to release in the colon is "Colonic Drug Delivery", Watts *et al*, Drug Development and Industrial Pharmacy, 23(9), 893-913 (1997).

The IBAT inhibitor may be formulated by conventional techniques.

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## Claims

1. A combination which comprises an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

2. A combination according to claim 1 wherein the metal salt is a calcium salt.

3. A combination according to either of claims 1 or 2 wherein the metal salt is calcium phosphate.

4. A combination according to any one of claims 1 - 3 wherein the IBAT inhibitor is a benzothiepine.

5. A combination according to any one of claims 1 - 3 wherein the IBAT inhibitor is selected from:
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine; and

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;
or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

6. A combination according to any one of claims 1 - 3 wherein the IBAT inhibitor is selected from:
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R)-α-carboxy-4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

7. The use of a combination according to any one of claims 1-6, in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

8. The use of a combination according to any one of claims 1-6, in the manufacture of a medicament for use in preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

9. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination according to any one of claims 1-6.

10. A method of preventing diarrhoea that would result from excess bile acids in the intestine following administration of an effective amount an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, to a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a combination according to any one of claims 1-6.

11. A pharmaceutical composition which comprises a combination according to any one of claims 1-6, in association with a pharmaceutically acceptable diluent or carrier.

12. A combination according to any one of claims 1-6 for use as a medicament.

13. A pharmaceutical composition which comprises a combination according to any one of claims 1-6, in association with a pharmaceutically acceptable diluent or carrier for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

14. The use of a combination according to any one of claims 1-6, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

15. A method of treating hyperlipidaemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a combination according to any one of claims 1-6.

16. A pharmaceutical composition which comprises a combination according to any one of claims 1-6, in association with a pharmaceutically acceptable diluent or carrier for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

17. The use of a combination according to any one of claims 1-6, in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

18. The use of a combination according to any one of claims 1-6 in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

19. The combination according to any one of claims 1-6 further comprising an HMG Co-A reductase inhibitor, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

20. The combination according to claim 19 wherein the HMG Co-A reductase inhibitor is fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, bervastatin,

dalvastatin, mevastatin and rosuvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

21. The combination according to any one of claims 1-6 further comprising a cholesterol absorption antagonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

22. The combination according to claim 21 wherein the a cholesterol absorption antagonist is SCH 58235.

23. The combination according to any one of claims 1-6 further comprising a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof.

24. The combination according to claim 23 wherein the PPAR alpha and/or gamma agonist is (S)-2-ethoxy-3-[4-(2-{4-methanesulphonyloxyphenyl}ethoxy)phenyl]propanoic acid and pharmaceutically acceptable salts thereof.

25. The use of a combination according to any one of claims 19-24 in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

26. The use of a combination according to any one of claims 19-24 in the manufacture of a medicament for use in the production of an IBAT inhibitory effect in a warm-blooded animal, such as man.

27. A method for producing an IBAT inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a composition according to any one of claims 19-24.

28 A pharmaceutical composition which comprises a combination according to any one of claims 19-24, in association with a pharmaceutically acceptable diluent or carrier.

29. A pharmaceutical composition which comprises a combination according to any one of claims 19-24, in association with a pharmaceutically acceptable diluent or carrier for use in producing an IBAT inhibitory effect, in a warm-blooded animal, such as man.

30. The use of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, in the manufacture of a medicament for the prevention of diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

31. The use of a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon, for the prevention of diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

32. A method of preventing diarrhoea that would result from excess bile acids in the intestine following administration of an IBAT inhibitor, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, which comprises administering to a patient in need thereof, a metal salt, wherein the metal salt is formulated to release in the terminal ileum, caecum and/or the colon.

# INTERNATIONAL SEARCH REPORT

Inte nal Application No
PCT/GB 03/02978

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/00 A61K33/14 A61K45/06 A61P1/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, MEDLINE, BIOSIS, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 02 32428 A (ASTRAZENECA UK LTD ;LINDQVIST ANN MARGRET (SE); ASTRAZENECA AB (SE) 25 April 2002 (2002-04-25) | 1,4-20, 25-32 |
| Y | page 12, line 15-23; claims | 1-32 |
| Y | WO 00 62810 A (LINDQVIST ANN MARGRET ;ASTRAZENECA AB (SE); ABRAHAMSSON BERTIL (SE) 26 October 2000 (2000-10-26) page 8, line 7-18; claims 16-21 | 1-32 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 September 2003 | 14/10/2003 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Herrera, S |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

national application No.
PCT/GB 03/02978

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 9-10, 15,17-18,25,27 and 31-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

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Continuation of Box I.2

The subject-matter of the present cliams is defined by means of the functional feature IBAT inhibitor. Because of the character of the functional feature, it cannot be guaranteed that the performed search is complete.
It cannot be excluded that compounds fulfilling the requirments of the functinal feature have not been identified as doing so in the prior art. If such compounds have not bee identified in the application either, they have not been convered by the search.
The search has been carried out, base on the functional feature per se as well as the examples given in the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Int. ial Application No
PCT/GB 03/02978

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | GOVERS M J ET AL: "Characterization of the adsorption of conjugated and unconjugated bile acids to insoluble, amorphous calcium phosphate." JOURNAL OF LIPID RESEARCH. UNITED STATES MAY 1994, vol. 35, no. 5, May 1994 (1994-05), pages 741-748, XP002256201 ISSN: 0022-2275 abstract | 1-32 |
| Y | WELBERG J W ET AL: "Calcium and the prevention of colon cancer." SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY. SUPPLEMENT. NORWAY 1991, vol. 188, 1991, pages 52-59, XP009018238 ISSN: 0085-5928 abstract | 1-32 |
| A | SPRONG R CORINNE ET AL: "Dietary calcium phosphate promotes Listeria monocytogenes colonization and translocation in rats fed diets containing corn oil but not milk fat." THE JOURNAL OF NUTRITION. UNITED STATES JUN 2002, vol. 132, no. 6, June 2002 (2002-06), pages 1269-1274, XP002256200 ISSN: 0022-3166 abstract | 1-32 |

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Information on patent family members

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PCT/GB 03/02978

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| WO 0062810 A | 26-10-2000 | AU 4633500 A | 02-11-2000 |
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